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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/368,076	08/03/1999	HONG JIN	7682-047	5091

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EXAMINER
LUCAS, ZACHARIAH

ART UNIT	PAPER NUMBER
1648	20

DATE MAILED: 10/22/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/368,076	JIN ET AL.	
	Examin r	Art Unit	
	Zachariah Lucas	1648	

-- Th MAILING DATE of this communication appears on the cover sheet with the corresp ndenc addr ss --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 June 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *36-43* is/are pending in the application.

4a) Of the above claim(s) *36-39* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *40-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Pri rity under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group II in Paper No. 18 is acknowledged.

2. Claims 36-39 withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 18.

Final Action

3. Applicant's amendment of the claims in paper number 15 (filed January 23, 2002) necessitated the new ground(s) of rejection presented in this Office action. Although no action has previously been made on the claims currently at issue in the case, there has been an action on the merits issued on the originally elected subject matter. As the applicant's chose to cancel the claims to originally elected subject matter, and to submit claims to new inventions, the applicants created the situation wherein new rejections are required in the case. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Specification

4. The disclosure is objected to because of the following informalities: In the discussion of how the cysteine to glycine substitutions were made, the applicant disclosed a set of primers used to create the substitutions. In the chart on page 89, the applicant disclosed a primer (SEQ ID NO: 52) that applicant identifies as used to create the C21G substitution. This disclosure is objected to because the nucleotide identified as having been substituted is the first nucleotide in the codon _GA. No single substitution in this stop codon could produce a cysteine. Further, the RSV genome sequence disclosed as SEQ ID NO: 1 of WO 98/02530 shows that the codon that should correspond to the identified substitution is "TGT" not "TGA." Thus, the disclosed primer is not correctly disclosed, because it should show two, not one, nucleic acid substitutions. It is assumed that the applicant intended either misstated the sequence, or neglected to indicate the second substitution. If either of these assumptions is correct, the examiner believes that the error would have been readily apparent by one of ordinary skill in the art, and that correction of the error would therefore not be New Matter in the application.

Appropriate correction is required.

Claim Objections

5. Claim 43 is objected to because of the following informalities: the claim improperly uses the word "or" rather than "and" between the last two members of the Markush Group. In identifying the members of the Markush Group, one should not use the alternative form. E.g. ...selected from the group of X, Y, **and** Z. Only where one is identifying alternative embodiments without using Markush Group formula should the claim read in the alternative form. E.g.: ...wherein R is A, B, C, **or** D. Appropriate correction is required.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 41 and 41 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated infectious RSV comprising a substitution of a glycine for cysteine residue 96, does not reasonably provide enablement for an isolated RSV wherein any cysteine residue has been substituted. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. While the application teaches use for attenuated RSV, which the substitution at cys96 appears to create (App. p. 90, lines 19-22), the same has not been shown for the remaining cysteines.

These other cysteines have been described as being part of a zinc binding motif. An early (1996) reference indicated that no functional characteristics of this structure had been identified. See, App., generally; and Worthington et al., PNAS 93:13754-13759, at 13759 (made of record

in paper 5, stating that the function of a related zinc binding domain is unknown). As no functional characteristics have been identified, and since without such knowledge, one skilled in the art would not know the effect of substitutions of the cysteines at residues 7, 15, or 21, or what properties such substitutions would bestow on the virus as a whole, such a person would not know how to use the recombinant RSV. This is the case because the virus would have different uses and properties (e.g. infectivity) depending on whether these substitutions did or did not inactivate the M2-1 protein. Since the applicant has not provided any evidence of what effect such mutations may have, they have not enabled one of ordinary skill in the art to use the invention without undue experimentation.

However, while the applicant has not provided any evidence as to what the effects of the substitutions of cysteine residues 7, 15, or 21 are, other art indicates that substitution of any of these cysteines is destructive of the functional integrity of the M2-1 proteins. Hardy et al., J. Virol., 74: 5880-5885 at 5884. Other art further indicates that the M2-1 protein is necessary to recovery of functional RSV particles. Collins et al., Virology, 259: 251-255 at 254. Thus, the art indicates that M2-1 protein is essential to create functional RSV, and further indicates that the claimed substitutions destroy the functionality of the protein. Given the applicant's lack of evidence demonstrating that such is not the case, the applicant has not enabled the claimed inventions to the extent that they read on the substitution of cysteine residues 7, 15, or 21.

8. Claim 43 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This claim describes an isolated and truncated RSV M2-1 polypeptide wherein stop codon

causing the truncation is at a position selected from the group consisting of nucleotide positions "7987-7989, 7990-7993, 8050-8052, 8053-8055, 8137-8139, [and] 8140-8142" (correction inserted). This claim is rejected for lack of enablement for the following reason.

The claim is identifying codons in the genes of the RSV virus. It is known that codons consist of three nucleic acids, each set of three nucleic acids encodes for a single amino acid. See e.g. Lodish et al., Molecular Cell Biology, pp. 120-121. Among the codons identified in the claim, is one of nucleotide positions 7990-7993. If this were so, this would be a codon of four nucleic acids. Such does not exist, therefore the applicant is not enabled for a protein encoded by such a nucleic acid.

9. Claims 42 and 43 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a deletion mutant of M2-1 wherein the truncation is at amino residues 178 or 179 (nucleic acids 8137-8139 or 8140-8142 respectively), does not reasonably provide enablement for any viable truncated M2-1 protein. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

While the applicants have shown that the M2-1 proteins truncated by the stops codons at positions 178 and 179 are effective attenuated proteins, the applicants have not shown that the other claimed truncated proteins are likewise effective. As these truncations remove more of the protein than the truncation described above (App. p. 92, lines 19-21), and as no indication is provided about what sequences of the protein are required for activity, there is no evidence that the other truncations will be operative. The applicant has stated that "viable M2-1 deletion mutants" are effective in attenuating RSV, and the specification has provided no utility or other

support for non-viable deletion mutants. Further, the art recognizes that the M2-1 protein is necessary for the recovery of functional RSV particles (see, Collins et al, supra; and Hardy et al., supra). Thus, as both the art and the specification indicate that at lest partially functional M2-1 proteins are required for viable RSV, and given the lack of guidance for making functional truncations, the specification has not enabled one skilled in the art to make or use any viable truncation of the M2-1 protein.

10. Claims 40 and 41 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claims read on substitutions in the M2-1 gene wherein the substitutions result in the substitution of a glycine, valine, aspartic acid, or alanine for a native cysteine residue. However, the specification of the application described only substitutions of glycine for the cysteines. Pp. 88-89. The examiner has noted that the applicant has cited a portion in the specification that they believed to support the claims. However, the citation listed as supporting claim 40 is merely a recitation that the applicant does not wish to be limited to the specific embodiments described in the specification, and provides no support or guidance to the embodiments of the claimed inventions. For claim 41, the applicant cites page 93, lines 3-9. There are no such lines the specification. Further, the claims of page 93 of the original specification do not provide adequate support for the relevant claims. Claim 20 (cancelled- p. 95) did claim a vaccine wherein the M2-1 gene is mutagenized by cysteine scanning mutagenesis. However, the specification seems to define cysteine scanning mutagenesis as substituting the cysteines with glycine. See, P. 88, lines 21-23 (where parenthetical identifies

the glycine substitutions as cysteine scanning mutagenesis without mentioning the substitution of any other residues for cysteine). Therefore, as the specification provides no support for embodiments where residues other than glycine are substituted for cysteine, the claims are rejected for lack of written description.

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. Claims 40 and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Worthington et al., supra, in view of Howorka et al. these claims read on RSV M2-1 proteins wherein the cysteine amino acids have been substituted with other amino acids. The claims identify these other amino acids as glycine, valine, aspartic acid, and alanine. No reason was provided in the specification for using these particular amino acids.

Worthington teaches that RSV shares a homologous zinc-binding domain of unknown functionality with other proteins (p. 13755). The reference also teaches that this zinc binding domain comprises three cysteine residues shared by all of the proteins. Id. These are the three cysteines at residues 7, 15, and 21 of RSV M2-1.The reference further teaches that the function of these zinc binding cites are unknown. P. 13759. However, the reference does not teach the substitution of these cysteines.

Howorka teaches that site directed mutagenesis is widely used for the determination of structural and functional relationships of proteins. See also, Frillingos et al, FASEB Journal, 12:1281-1299. From Howorka, it would be obvious to one of ordinary skill in the art to use site-directed mutagenesis of a particular residue in a defined sequence in order to determine the function of that sequence. Although the references do not disclose the substitution of cysteine, or the use of the claimed residues to do so, it would have been obvious to one of ordinary skill in the art to use any non-cysteine residue in the place of cysteine in such a method.

As Worthington identifies the three cysteines and indicates that although these cysteines share a structural relationship with cysteines of other proteins, the function is not known of the sequence comprising them, and Howorka describes a method that could be easily adapted for use in determining that function, it would have been obvious to one of ordinary skill in the art to combine the references to yield RSV M2-1 proteins wherein these cysteines had been substituted with another amino acid residue. The motivation to do so would be to determine the function of these cysteines. This is deemed an adequate motivation for the combination in the present case as the applicant have also failed to describe both the function of the zinc binding motif, and the effect of the substitutions of these cysteines. As any person skilled in the art would not know how to use the claimed cysteine mutants until after they had determined how the substitutions affects the activity of the protein, the applicant has in essence required those in the art to use the same site-directed mutagenesis to determine the function of the protein sequence.

Conclusion

13. No Claims are allowed.

14. The following prior art reference is made of record and is considered pertinent to applicant's disclosure. However, while relevant they are also not used as a basis for rejection for the stated reasons.

> WO 97/12032, naming Peter Collins as inventor. This reference is relevant in that it teaches that the M2-1 protein is required for processive transcription of the viral genome. Pp. 13-14. Thus, the reference teaches that the complete M2-1 gene is necessary for infectivity and teaches away from the attenuation of the virus by deleting or truncating the protein or gene encoding it.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachariah Lucas whose telephone number is 703-308-4240. The examiner can normally be reached on Monday-Friday, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on 703-308-4027. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Z. Lucas
Patent Examiner
October 17, 2002

JAMES HOUSEL 10/20/02
SUPERVISORY PATENT EXAMINER
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